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HARD-SOFT AFFINITY INVERSION: DEHALOGENATION OF α-HALOKETONES

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Treatment of α-bromo and α-iodoketones with aluminum chloride and ethanethiol gave rise to dithioacetals of the corresponding dehalogenated ketones. α-Chloro and α-fluoroketones were also dehalogenated with the same reagent system through *in situ* hard-soft affinity inversion.

Almost all chemical bonds, except for special ones like the symmetrically substituted carbon-carbon bond, involve the hard-soft dissymmetry as well as the charge dissymmetry. Reversal of the charge dissymmetry by modifying the structural unit has been termed umpolung[1] and has played an important role as one of heuristic principles in synthetic organic chemistry.[2] However, little attention has been paid for the inversion of hard-soft affinity by modifying the structure as a method of choice in synthetic organic chemistry. Here, we report the successful application of the principle of the hard-soft affinity inversion to dehalogenation of α-haloketones.

Since α-bromoketones possess a hard center, carbonyl oxygen, and a soft center, bromine atom, pertinent combination systems consisting of a hard acid and a soft nucleophile[3] can be utilized for the reductive debromination of α-bromoketones as shown in Fig. 1. A wide range of methods along these lines is available in the literature.[4] On the other hand, dechlorination and defluorination in this fashion are unfavorable because Cl^+ and F^+ are relatively hard as compared with I^+ and Br^+. However a hard-soft affinity can be inverted by dithioacetalization, where the hard oxygen atom is replaced by sulfur which is regarded as a soft atom. As a consequence, the electron movement opposite to that shown in Fig. 1 is expected to end up with the reductive removal of X in the dithioacetals

(Fig. 2). Aluminum chloride as a hard acid and ethanethiol as a soft base (nucleophile) seem to be most suitable combination for the required two step process in one pot, because this combination is expected to convert α-haloketones into the corresponding dithioacetals,[5] whereby *in situ* hard-soft affinity inversion is accomplished.

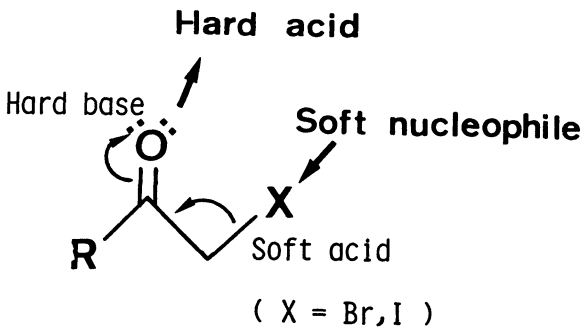


Fig. 1.

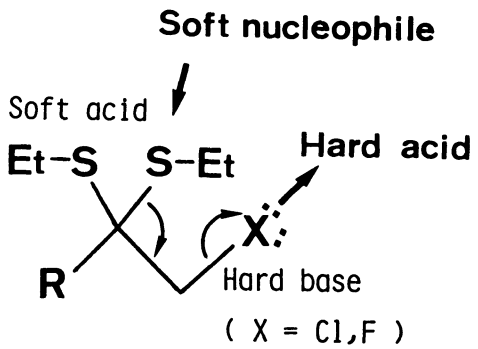


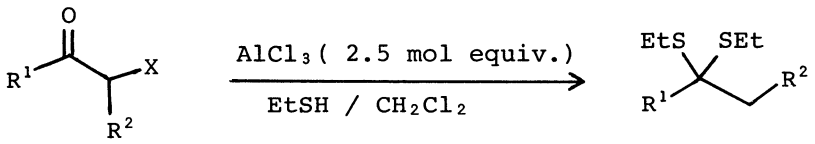
Fig. 2.

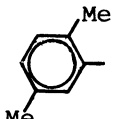
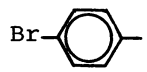
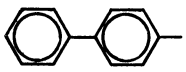
The results are summarized in the Table. Treatment of α-chloro and α-fluoroketones with aluminum chloride and ethanethiol in dichloromethane afforded the corresponding dehalogenated dithioacetals in satisfactory yields. Reductive debromination and deiodination took place under the similar reaction conditions, although the removal of bromine or iodine in the mode as shown in Fig. 2 is not a favorable process because Br^+ and I^+ are regarded as a soft acid. This might be attributed to the difference in mechanism which depends upon the halogen atom to be reductively removed. Thus, α-bromo and α-iodoketones 5 and 9 afforded acetophenone in 73% and 60% yield respectively, when diethyl sulfide was used in place of ethanethiol under the comparable conditions listed in the Table. This may suggest that the original hard-hard and soft-soft affinity shown in Fig. 1 are operative in these cases. α-Fluoro and α-chloroketones 1 and 3, on the other hand, were recovered unchanged under the conditions with diethyl sulfide as a soft nucleophile, which indicated the necessity of the initial formation of the dithioacetal. Thus, the expected hard-soft affinity inversion *in situ* occurred in these cases, followed by the subsequent conversion to the final product.

Although a numerous number of reductive dehalogenation of α-haloketones

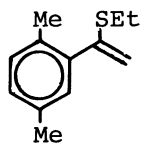
have been reported,[4] no practically applicable method of defluorination is available in the literature.[6] A unique feature of the present system opened a new way to the reductive removal of fluorine in α-fluoroketones.

Table 1. Dehalogenation of α-Haloketones[a]



α-Haloketone				Reaction time	Yield
No.	R^1	R^2	X	min	%
1	Ph	H	F	20	67
2		H	F	20	72[b]
3	Ph	H	Cl	10	77
4	$-(CH_2)_5-$		Cl	15	69
5	Ph	H	Br	20	98
6		H	Br	30	86
7		H	Br	20	75
8	$-(CH_2)_5-$		Br	15	56
9	Ph	H	I	5	>99

a) Substrate (1 mmol) in dichloromethane (2 ml) and ethanethiol (0.4 ml) was stirred with aluminum chloride (1.5 equiv.) at 0°C under nitrogen. b) A mixture of 10 (53%), 11 (8%), and 12 (11%).



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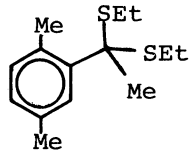

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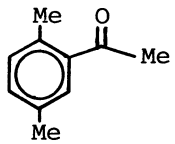

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References

1) D. Seebach and M. kolb, Chem. Ind., 1974, 687.

2) D. Seebach, Angew. Chem., Int. Ed. Engl., 18, 239 (1979); B.-T. Gröbel and D. Seebach, Synthesis, 1977, 357.

3) M. Node, K. Ohta, T. Kajimoto, K. Nishide, E. Fujita, and K. Fuji, Chem. Pharm. Bull., 31, 4178 (1983), and references cited therein.

4) For an extensive review, see A. R. Pinder, Synthesis, 1980, 425.

5) B. S. Oug, Tetrahedron Lett., 21, 4225 (1980).

6) α,α,α-Trifluoroacetophenone was reduced to a mixture of acetophenone and acetophenone pinacol electrolytically (J. H. Stocker and R. M. Jenevein, J. Chem. Soc., Chem. Commun., 1968, 934). The Clemmensen reduction conditions can affect the recuctive removal of fluorine with a concomitant reduction of the carbonyl group [E. J. P. Fear, J. Thrower, and J. Veitch, J. Appl. Chem., 5, 589 (1955)].

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